(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 3 777 834 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
16.02.2022 Bulletin 2022/07

(21) Application number: **20198921.7**

(22) Date of filing: **30.05.2013**

(51) International Patent Classification (IPC):
A61K 9/00 *(2006.01)* ***A61M 5/28*** *(2006.01)*
A61M 5/31 *(2006.01)* ***A61M 5/315*** *(2006.01)*
A61P 43/00 *(2006.01)* ***A61P 27/02*** *(2006.01)*

(52) Cooperative Patent Classification (CPC):
A61M 5/001; A61M 5/28; A61M 5/31505; A61M 5/31513; A61P 27/02; A61P 43/00;
A61M 5/3137; A61M 2005/3104; A61M 2005/3139; A61M 2005/31508

(54) **SYRINGE**

SPRITZE

SERINGUE

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME

(30) Priority: **01.06.2012 EP 12170628**

(43) Date of publication of application:
17.02.2021 Bulletin 2021/07

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
19161189.6 / 3 536 310
13727570.7 / 2 854 762

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Description

[0001] The present invention relates to a syringe, particularly to a small volume syringe suitable for ophthalmic injections. The invention also extends to a method of assembling such a syringe.

[0002] Many medicaments are delivered to a patient in a syringe from which the user can dispense the medicament. If medicament is delivered to a patient in a syringe it is often to enable the patient, or a caregiver, to inject the medicament. It is important for patient safety and medicament integrity that the syringe and the contents of that syringe are sufficiently sterile to avoid infection, or other, risks for patients. Sterilisation can be achieved by terminal sterilisation in which the assembled product, typically already in its associated packaging, is sterilised using heat or a sterilising gas.

[0003] For small volume syringes, for example those for injections into the eye in which it is intended that less than about 0.1ml of liquid is to be injected, the sterilisation can pose difficulties that are not necessarily associated with larger syringes. Changes in pressure, internal or external to the syringe, can cause parts of the syringe to move unpredictably, which may alter sealing characteristics and potentially compromise sterility. Incorrect handling, including assembly, of the syringe can also pose risks to product sterility.

[0004] WO2011/006877 discloses methods and systems for the terminal sterilization and surface decontamination of prefilled containers (e.g. syringes) containing sensitive drug products, such as proteins (e.g. ranibizumab) which may be temperature or radiation sensitive, and thus not suitable for terminal sterilization by classical methods involving steam or gamma rays. The methods include terminal sterilization by exposing prefilled containers in secondary packaging to tunable-beta radiation, or to controllable vaporized-hydrogen peroxide.

[0005] WO2007/035621 discloses a device for use in intravitreal administration of ocular agents. The device comprises: a syringe comprising a barrel having a proximal and a distal end and a volume of 1 mL or less, adapted to contain an injection solution wherein said solution contains a subvisible particulate count of less than 50 particles per mL when contained in the barrel; a Luer lock tip attached to the distal end of the barrel; a needle having a gauge of 27 or narrower, comprising a cannula attached to a Luer lock hub for attachment to the Luer lock tip, wherein the needle requires a penetration force of less than 100 g to penetrate scleral tissue; a syringe tip cap attached to the Luer lock tip for sealing a solution contained in the barrel; and a needle tip shield adapted to attach to the Luer lock hub and enclose the needle.

[0006] US2006/0293270 discloses a method for treating an ocular disease (such as macular degeneration) in a patient comprising administering less than 0.3 mg of the Macugen™ anti-VEGF aptamer, for instance by intravitreal injection of 90pL of aptamer solution.

[0007] The present invention provides a terminally-sterilised syringe, the syringe comprising a body, a stopper and a plunger, the body comprising an outlet at an outlet end and the stopper being arranged within the body such that a front surface of the stopper and the body define a variable volume chamber from which a fluid can be expelled though the outlet, the plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion, the plunger contact surface arranged to contact the stopper but not couple thereto, such that the plunger can be used to force the stopper towards the outlet end of the body, reducing the volume of the variable volume chamber, but not to move the stopper away from the outlet end.

[0008] Providing a plunger which does not couple to the stopper reduces the chances for incorrect handling of the syringe as the plunger can be withdrawn from the syringe without movement of the stopper away from the outlet end. This prevents a user from accidentally moving the plunger (and therefore a stopper connected thereto) and causing non-sterile air (or other fluid) to be drawn into the syringe, or causing movement of the stopper to a non-sterile area. It has also been found that creating a connection between a plunger to a stopper during assembly, using for example a screwing action or a pushfit action, can distort the stopper in an unpredictable manner which may compromise the sealing and/or sterility of the final product, or may increase pressure in the variable volume chamber which could cause fluid leakage from the outlet end.

[0009] The body of the syringe may be a substantially cylindrical shell, or may include a substantially cylindrical bore with a non-circular outer shape. The outlet end of the body includes an outlet through which a fluid housed within the variable volume chamber can be expelled as the volume of said chamber is reduced. The outlet may comprise a projection from the outlet end through which extends a channel having a smaller diameter than that of the variable volume chamber. The outlet may be adapted, for example via a luer lock type connection, for connection to a needle or other accessory such as a sealing device which is able to seal the variable volume chamber, but can be operated, or removed, to unseal the variable chamber and allow connection of the syringe to another accessory, such as a needle. Such a connection may be made directly between the syringe and accessory, or via the sealing device. The body extends along a first axis from the outlet end to a rear end.

[0010] The body may be made from a plastic material or from glass, or from any other suitable material and may include indicia on a surface thereof to act as an injection guide.

[0011] The stopper may be made from rubber, silicone or other suitable resiliently deformable material. The stopper provides a sealing function by defining the rear of the variable volume chamber with a fluid tight seal which also provides a sterility seal. The stopper may be substantially cylindrical and the stopper may include one or more circumferential ribs around an outer surface of

the stopper, the stopper and ribs being dimensioned such that the ribs form a substantially fluid tight seal with an internal surface of the syringe body. The front surface of the stopper may be any suitable shape, for example substantially planar, or substantially conical. The stopper may be substantially solid or may include recesses. The rear surface of the stopper may include a substantially central recess which may be any shape provided the sealing function of the stopper is not compromised. Said central recess may be substantially cylindrical in shape or said central recess may include an initial bore having a first diameter, the initial bore leading from the rear surface into the stopper to an inner recess having a second diameter, the second diameter being larger than the first diameter. Such a central recess could be used to connect a plunger to the stopper using a snap fit feature in a known manner. Such a design allows a substantially standard stopper design to be used and this can reduce the parts cost for the syringe. Also, it is noted that removing material from the central portion of the stopper, where it is not needed for the stopper to function as required, reduces the stopper weight and reduces the amount of material needed to manufacture the stopper. The stopper may be substantially rotationally symmetric about an axis through the stopper.

[0012] The plunger comprises a plunger contact surface and extending from that a rod extends from the plunger contact surface to a rear portion. The rear portion may include a user contact portion adapted to be contacted by a user during an injection event. The user contact portion may comprise a substantially disc shaped portion, the radius of the disc extending substantially perpendicular to the axis along which the rod extends. The user contact portion could be any suitable shape. The axis along which the rod extends may be the first axis, or may be substantially parallel with the first axis.

[0013] The plunger contact surface is adapted to make contact with the rear surface of the stopper, but not couple thereto. The plunger contact surface may be substantially planar and may be substantially circular in shape. The plunger contact surface may be substantially circular with an outer diameter less than the internal diameter of the body. The diameter of the plunger contact surface may be substantially equal to the diameter of the rear surface of the stopper with which it is to make contact. The plunger contact surface may be adapted to present a substantially rotationally symmetrical surface to the rear surface of the stopper as this assists in providing a repeatable and evenly distributed force to the stopper during use which can help to prevent distortions. The plunger contact surface may not be planar and may comprise an annular contact surface to contact the stopper at or adjacent an out edge thereof. The plunger contact surface may comprise a plurality of arms which extend from the plunger rod to make contact with the stopper. The plunger contact surface may be substantially rotationally symmetrical in any of the above, or other, embodiments.

[0014] The rod may have a round or cross-form cross-section. A cross-form cross section may be formed from ribs extending along at least part of the rod. The ribs may extend substantially parallel with the axis along which the rod extends. The cross-form cross section provides rigidity to the rod without significantly increasing manufacturing complexity.

[0015] The rod may be manufactured from any suitable material, or combination of materials, and in one embodiment is made from a plastic material. The rod may be substantially rigid under expected use conditions. Although some flexing of the materials in the plunger is unavoidable in a bulk manufactured product, it is advantageous that the rod cannot flex significantly during use, particularly for low volume, accurate, injections as any flexing could lead to unpredictable dosing results.

[0016] The syringe may include a backstop arranged at a rear portion of the body. The backstop may be removable from the syringe. If the syringe body includes terminal flanges at the end opposite the outlet end the backstop may be configured to substantially sandwich terminal flanges of the body as this prevent movement of the backstop in a direction parallel to the first axis.

[0017] The rod may comprise at least one rod shoulder directed away from the outlet end and the backstop may include a backstop shoulder directed towards the outlet end to cooperate with the rod shoulder to substantially prevent movement of the rod away from the outlet end when the backstop shoulder and rod shoulder are in contact. Restriction of the movement of the rod away from the outlet end can help to maintain sterility during terminal sterilisation operations, or other operations in which the pressure within the variable volume chamber or outside the chamber may change. During such operations any gas trapped within the variable volume chamber, or bubbles that may form in a liquid therein, may change in volume and thereby cause the stopper to move. Movement of the stopper away from the outlet could result in the breaching of a sterility zone created by the stopper. This is particularly important for low volume syringes where there are much lower tolerances in the component sizes and less flexibility in the stopper. The term sterility zone as used herein is used to refer to the area within the syringe that is sealed by the stopper from access from either end of the syringe. This may be the area between a seal of the stopper, for example a circumferential ridge, closest to the outlet and a seal of the stopper, for example a circumferential ridge, furthest from the outlet. The distance between these two seals defines the sterility zone of the stopper since the stopper is installed into the syringe barrel in a sterile environment.

[0018] A terminal sterilisation process used to sterilise the complete article may use a known process such as an Ethylene Oxide or a Hydrogen Peroxide sterilisation process.

[0019] The inclusion of one or more circumferential ribs on the stopper can alter the force required to cause the stopper to move from a stationary position and can also alter the sealing properties of the stopper. To further as-

sist in maintaining sterility during the operations noted above the stopper may comprise at least a front circumferential rib and a rear circumferential rib and those ribs may be separated in a direction along the first axis by at least 3mm, by at least 3.5 mm, by at least 3.75mm or by 4mm or more. One or more additional ribs (for example 2, 3, 4 or 5 additional ribs, or between 1-10, 2-8, 3-6 or 4-5 additional ribs) may be arranged between the front and rear ribs. In one embodiment there are a total of three circumferential ribs.

[0020] A stopper with such an enhanced sterility zone can also provide protection for the injectable medicament during a terminal sterilisation process. Some medicaments, example a biological medicament, could be damaged by exposure to Ethylene Oxide. More ribs on the stopper, or a greater distance between the front and rear ribs, can reduce the potential exposure of the medicament to the sterilising agent.

[0021] The rod shoulder may be arranged within the external diameter of the rod, or may be arranged outside the external diameter of the rod. By providing a shoulder that extends beyond the external diameter of the rod, but still fits within the body, the shoulder can help to stabilise the movement of the rod within the body by reducing movement of the rod perpendicular to the first axis. The rod shoulder may comprise any suitable shoulder forming elements on the rod, but in one embodiment the rod shoulder comprises a substantially disc shaped portion on the rod.

[0022] In one embodiment of the syringe, when arranged with the plunger contact surface in contact with the stopper and the variable volume chamber is at its intended maximum volume there is a clearance of no more than about 2mm between the rod shoulder and backstop shoulder. In some embodiments there is a clearance of less than about 1.5 mm and in some less than about 1mm. This distance is selected to substantially limit or prevent excessive rearward (away from the outlet end) movement of the stopper.

[0023] In one embodiment the variable volume chamber has an internal diameter greater than 5mm or 6mm and less than 3mm or 4mm. The internal diameter may be between 3mm and 6mm, or between 4mm and 5mm.

[0024] The syringe is dimensioned so as to have a nominal maximum fill volume of between about 0.25ml and 0.75ml, or between 0.4ml and 0.6ml. The length of the body of the syringe may be less than 70mm, less than 60mm or less than 50mm. In one embodiment the length of the syringe body is between 45mm and 50mm, the internal diameter is between 4mm and 5mm and the fill volume is between 0.1ml and 0.3ml of liquid.

[0025] The syringe is suitable for ophthalmic injections, and as such has a suitably small volume. The syringe may be adapted for ophthalmic injections. The syringe may also be silicone free, or substantially silicone free, or may comprise a low level of silicone as lubricant. In one embodiment, the syringe may meet USP789.

[0026] The variable volume chamber of the syringe is filled with an injectable medicament comprising an active suitable for the treatment of an ocular disease. Examples of such ocular diseases include choroidal neovascularisation, age-related macular degeneration (both wet and dry forms), macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy. In one embodiment, the medicament comprises a biologic active. The biologic active may be an antibody (or fragment thereof) or a non-antibody protein. In one embodiment the medicament comprises a VEGF antagonist. Suitable VEGF antagonists include ranibizumab (Lucentis™), bevacizumab (Avastin™), aflibercept (Eylea™, also known as VEGF-Trap Eye), conbercept (KH902 from Chengdu Kanghong Biotechnologies Co. Ltd, described as FP3 in WO2005/121176) and the related glycoform KH906 or pazopanib (from GlaxoSmithKline).

[0027] In one embodiment, the syringe is filled with between about 0.01ml and about 2ml (for example between about 0.05ml and about 1ml, between about 0.1ml and about 0.5ml) of an injectable medicament. Of course, typically a syringe is filled with more than the desired dose to be administered to the patient, to take into account wastage due to "dead space" within the syringe and needle. Thus, in one embodiment, the syringe is filled with a dosage volume (i.e. the volume of medicament intended for delivery to the patent) of between about 0.01ml and about 2ml (e.g. between about 0.05ml and about 1ml, between about 0.1ml and about 0.5ml) of an injectable medicament. For example, for Lucentis, the dosage volume is 0.05ml or 0.03ml (0.5mg or 0.3mg) of a 10mg/ml injectable medicament solution; for Eylea, the dosage volume is 0.05ml of a 40mg/ml injectable medicament solution.

[0028] As noted above, when the syringe contains a medicament solution the outlet may be reversibly sealed to maintain sterility of the medicament. This sealing may be achieved through the use of a sealing device as is known in the art. For example the OVS™ system which is available from Vetter Pharma International GmbH. The sealing of the outlet should be such that that sterility of the contents of the variable volume chamber can be maintained until such time as the stopper is moved to breach the sterility seal or the outlet is unsealed.

[0029] By providing a plunger that does not couple with the stopper a new method of assembly is made possible and so the invention further provides a method of assembling a syringe, the method comprising the steps of:

i) providing a body and a stopper, the body comprising an outlet at an outlet end and the stopper being arranged within the body such that a front surface of the stopper and the body define a variable volume chamber from which a fluid can be expelled though the outlet, the outlet being releasably sealed and the

variable volume chamber containing a medicament; and

ii) providing a plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion and arranging the plunger contact surface and at least part of the plunger within the body without coupling the plunger to the stopper.

[0030] The method may further comprise an additional step, step iii), of filling the variable volume chamber of the syringe, which may be filled with any suitable injectable medicament. In one embodiment the variable volume chamber is filled with an injectable medicament suitable for the treatment of an ocular disease. Examples of such ocular diseases include choroidal neovascularisation, age-related macular degeneration (both wet and dry forms), macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy. In one embodiment, the medicament comprises a biologic active. The biologic active may be an antibody (or fragment thereof) or a non-antibody protein. In one embodiment the medicament comprises a VEGF antagonist. Suitable VEGF antagonists include ranibizumab (Lucentis™), bevacizumab (Avastin™), aflibercept (Eylea™, also known as VEGF-Trap Eye), conbercept (KH902 from Chengdu Kanghong Biotechnologies Co. Ltd, described as FP3 in WO2005/121176) and the related glycoform KH906 or pazopanib (from GlaxoSmith-Kline).

[0031] It should be noted that steps ii) and iii) above may be carried out in either order. Thus the method may comprise, in sequence, steps i), ii), iii) or steps i), iii), ii) or steps iii), i), ii).

[0032] The method may further comprise a step iv) of packaging the assembled syringe in a substantially sealed package. The method may further comprise a terminal sterilisation step, step v), following packaging. The terminal sterilisation step may comprise known techniques such as Ethylene Oxide sterilisation of Hydrogen Peroxide sterilisation.

[0033] The invention also extends to a sealed package containing a sterile pre-filled syringe substantially as described herein.

[0034] If the rod comprises a rod shoulder as described above and the syringe includes a removable backstop as described the backstop may be coupled to the syringe body after the plunger has been arranged in the body and the rod shoulder is arranged between the outlet end and the backstop shoulder. By ensuring that the rod shoulder is arranged between the outlet end and the backstop shoulder when the backstop is coupled to the device a complex mechanism for enabling the movement of the rod shoulder past the backstop shoulder after coupling the backstop to the syringe is avoided.

[0035] In one embodiment step i) and iii) are carried out in a sterile, or substantially sterile, environment. At some point between the filling step and the final assembly being sealed into packaging the syringe is removed from the sterile, or substantially sterile, environment. A terminal sterilisation step can then be conducted on the packaged product.

[0036] In one embodiment of the method the plunger rod is dropped into the syringe body. This is a simple operation and makes use of gravity rather than any automated assembly equipment. This is made possible because the rod does not need to be manipulated or forced to couple with the stopper.

[0037] The invention also provides a plunger suitable for use in the syringe or method described above.

[0038] It should be understood that throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", implies the inclusion of the stated integer or step, or group of integers or steps. The term "comprising" encompasses "including" as well as "consisting" e.g. a composition "comprising" X may consist exclusively of X or may include something additional e.g. X + Y. It should also be understood that, unless not physically possible, features described in connection with one embodiment can be used alone, or in combination with one or more features described in connection with the same embodiment or one or more other embodiments. The term "about" in relation to a numerical value x is optional and means, for example, x +/- 10%.

[0039] The invention will now be further described, by way of example only, with reference to the following drawings in which:

Figure 1 shows a side view of a syringe;

Figure 2 shows a cross section of a top down view of a syringe;

Figure 3 shows a view of a plunger;

Figure 4 shows a cross section though a plunger;

Figure 5 shows a stopper; and

Figure 6 shows a flowchart of the assembly process.

[0040] Figure 1 shows a view from a side of a syringe 1 comprising a body 2, plunger 4, backstop 6 and a sealing device 8.

[0041] Figure 2 shows a cross section through the syringe 1 of Figure 1 from above. The syringe 1 is suitable for use in an ophthalmic injection. The syringe 1 comprises a body 2, a stopper 10 and a plunger 4. The syringe 1 extends along a first axis A. The body 2 comprises an outlet 12 at an outlet end 14 and the stopper 10 is arranged within the body 2 such that a front surface 16 of

the stopper 10 and the body 2 define a variable volume chamber 18. The variable volume chamber 18 contains an injectable medicament 20 comprising ranibizumab. The injectable fluid 20 can be expelled though the outlet 12 by movement of the stopper 10 towards the outlet end 14 thereby reducing the volume of the variable volume chamber 18. The plunger 4 comprises a plunger contact surface 22 at a first end 24 and a rod 26 extending between the plunger contact surface 22 and a rear portion 25. The plunger contact surface 22 is arranged to contact the stopper 10 but not couple thereto, such that the plunger 4 can be used to move the stopper 10 towards the outlet end 14 of the body 2. Such movement reduces the volume of the variable volume chamber 18 and causes fluid therein to be expelled though the outlet.

[0042] However, since the plunger 4 is not coupled to the stopper 10 it is not possible to use the plunger 4 to move the stopper 10 away from the outlet end 14.

[0043] The backstop 6 is attached to the body 2 by coupling to a terminal flange 28 of the body 2. The backstop 6 includes sandwich portion 30 which is adapted to substantially sandwich at least some of the terminal flange 28 of the body 2. The backstop 6 is adapted to be coupled to the body 2 from the side by leaving one side of the backstop 6 open so that the backstop 6 can be fitted to the syringe 2.

[0044] The body 2 defines a substantially cylindrical bore 36 which has a bore radius. The rod 26 comprises a rod shoulder 32 directed away from the outlet end 14. The rod shoulder 32 extends to a rod shoulder radius from the first axis A which is such that it slightly less than the bore radius so that the shoulder fits within the bore 36. The backstop 6 includes a backstop shoulder 34 directed towards the outlet end 14. The shoulders 32,34 are configured to cooperate to substantially prevent movement of the rod 26 away from the outlet end 14 when the backstop shoulder 34 and rod shoulder 32 are in contact. The backstop shoulder 34 extends from outside the bore radius to a radius less than the rod shoulder radius so that the rod shoulder 32 cannot pass the backstop shoulder 34 by moving along the first axis A. In this case the rod shoulder 32 is substantially disc, or ring, shaped and the backstop shoulder 34 includes an arc around a rear end 38 of the body 2.

[0045] The backstop 6 also includes two finger projections 40 which extend in opposite directions away from the body 2 substantially perpendicular to the first axis A to facilitate manual handling of the syringe 1 during use.

[0046] In this example the syringe comprises a 0.5ml body 2, that is a body with a notional maximum fill volume of about 0.5ml, filled with between about 0.1 and 0.3 ml of an injectable medicament 20 comprising a 10mg/ml injectable solution comprising ranibizumab. The syringe body 2 has an internal diameter of about between about 4.5mm and 4.8mm, a length of between about 45mm and 50mm.

[0047] The plunger 4 and stopper 10 will be described in more detail with reference to later figures.

[0048] Figure 3 shows a perspective view of the plunger 4 of Figure 1 showing the plunger contact surface 22 at the first end 24 of the plunger 4. The rod 26 extends from the first end 24 to the rear portion 25. The rear portion 25 includes a disc shaped flange 42 to facilitate user handling of the device. The flange 42 provides a larger surface area for contact by the user than a bare end of the rod 26.

[0049] The rod 26 comprises ribs 44 which extend along the rod 26, the ribs forming a cross-form cross section for the rod 26 as shown in more detail in subsequent figures. The rod 26 comprises a disc shaped portion 46, the disc shaped portion 46 extending radially beyond the ribs 44 and also forming the rod shoulder 32.

[0050] The ribs 44 may be substantially solid, or may include gaps 48. The disc portion 46 may be solid, or may include gaps 50. Gaps 48,50 may be used to facilitate gas flow within the body 2 if necessary for sterilization, or other, purposes.

[0051] Figure 4 shows a cross section though a syringe body 2 and rod 26. The rod 26 includes four longitudinal ribs 44 and the angle between the ribs is 90°.

[0052] Figure 5 shows a detailed view of a stopper 10 showing a conical shaped front surface 16 and three circumferential ribs 52,54,56 around a substantially cylindrical body 58. The axial gap between the first rib 52 and the last rib 56 is about 3mm. The rear surface 60 of the stopper 10 includes a substantially central recess 62. The central recess 62 includes an initial bore 64 having a first diameter. The initial bore 64 leading from the rear surface 60 into the stopper 10 to an inner recess 66 having a second diameter, the second diameter being larger than the first diameter.

[0053] Figure 6 shows a flow chart for the assembly of a syringe 1. In Step 1 a prefilled body 2 is provided. The prefilled body comprises a body 2 filled with an injectable medicament 20 comprising ranibizumab, although other medicaments could be used in addition or instead, or a placebo solution could be used. A stopper 10 is arranged in the body 2 to form a variable volume chamber 18 and the outlet 12 is sealed with a sealing device 8.

[0054] In Step 2 a plunger 4 is arranged in the body 2. In one embodiment the plunger 4 is dropped into the body 2. This may be by gravity alone, or the plunger may be placed into the body 2 using a machine or human and the body then oriented so that the plunger 4 falls into the body 2 until the plunger contact surface 22 makes contact with the stopper 10.

[0055] In Step 3 a backstop 6 is coupled to the terminal flange 28 of the body. The backstop 6 and rod being arranged such that the rod shoulder 32 is located between the outlet end of the body and the backstop shoulder 34.

[0056] In Step 4 the syringe is sealed into a package and in Step 5 the package and its contents is sterilised in a terminal sterilisation process. The terminal sterilisation process may use known process such as an Ethylene Oxide or a Hydrogen Peroxide sterilisation process.

[0057] It should be understood that the invention has been described above by way of example only and that modifications in detail can be made without departing from the scope of the claims.

Claims

1. A terminally-sterilised ophthalmic syringe, the syringe comprising a body (2), a stopper (10) and a plunger (4), the body comprising an outlet (12) at an outlet end (14) and the stopper (10) being arranged within the body (2) such that a front surface (16) of the stopper (10) and the body (2) define a variable volume chamber (18) from which a fluid can be expelled though the outlet (12), the plunger (4) comprising a plunger contact surface (22) at a first end (24) and a rod (26) extending between the plunger contact surface (22) and a rear portion (25);

   wherein the variable volume chamber (18) is filled with an injectable medicament comprising an active suitable for the treatment of an ocular disease;
   characterised in that:

   the plunger contact surface (22) is arranged to contact the stopper (10) but not couple thereto, such that the plunger (4) can be used to force the stopper (10) towards the outlet end (14) of the body (2), reducing the volume of the variable volume chamber (18), but not to move the stopper (10) away from the outlet end (14); and
   the syringe is dimensioned so as to have a nominal maximum fill volume of between 0.25 mL and 0.75 mL, or between 0.4 mL and 0.6 mL.

2. The syringe of claim 1, wherein the outlet (12) is reversibly sealed.

3. The syringe of any preceding claim, wherein the rod (26) comprises at least one rod shoulder (32) directed away from the outlet end (14) and the syringe includes a backstop arranged at a rear portion (25) of the body (2), the backstop including a backstop shoulder (34) directed towards the outlet end (14) to cooperate with the rod shoulder (32) to substantially prevent movement of the plunger rod (26) away from the outlet end (14) when the backstop shoulder (34) and rod shoulder (32) are in contact.

4. The syringe of any preceding claim, wherein (a) the rod shoulder (32) is arranged within the external diameter of the rod (26); and/or (b) the rod shoulder (32) comprises a substantially disc shaped portion (46) on the rod (26), wherein the disc shaped portion (46) optionally includes gaps (50).

5. The syringe of claim 3 or claim 4, wherein the backstop is removable from the syringe; and optionally wherein the backstop is configured to substantially sandwich terminal flanges (28) of the body.

6. The syringe of any one of claims 3 to 5 wherein, when arranged with the plunger contact surface (22) in contact with the stopper (10) and the variable volume chamber (18) is at its intended maximum volume, there is a clearance of no more than 2mm between the rod shoulder (32) and backstop shoulder (34).

7. The syringe of any preceding claim, wherein: (a) the variable volume chamber (18) has an internal diameter between 3 mm and 6 mm; (b) the syringe is dimensioned so as to have a nominal maximum fill volume of between 0.4 mL and 0.6 mL; and/or (c) the length of the body (2) of the syringe is less than 70 mm, for instance less than 60 mm or less than 50 mm.

8. The syringe of any preceding claim, wherein the length of the syringe body (2) is between 45 mm and 50 mm, the internal diameter is between 4mm and 5mm, and the fill volume is between 0.1 mL and 0.3 mL of liquid.

9. The syringe of any preceding claim, wherein: (a) the stopper (10) provides a sealing function by defining the rear of the variable volume chamber (18) with a fluid tight seal, which also provides a sterility seal; and/or (b) the stopper (10) contains one or more circumferential ribs e.g. three circumferential ribs (52, 54, 56).

10. The syringe of any preceding claim, wherein the stopper (10) contains at least a front circumferential rib (52) and a rear circumferential rib (56) which are separated in a direction along an axis (A) from the outlet end (14) to the rear end (38) by at least 3 mm.

11. The syringe of any preceding claim, wherein the plunger (4) which does not couple to the stopper (10) prevents a user from accidentally moving the plunger (4) and a stopper connected thereto (10) and causing non-sterile air or other fluid to be drawn into the syringe, or causing movement of the stopper (10) to a non-sterile area.

12. The syringe of any preceding claim, wherein: (a) the movement of the rod (26) away from the outlet end (14) is restricted; and/or (b) the plunger contact surface (22) is a substantially planar disc, and the plunger contact surface (22) contacts a rear surface of the stopper (10).

13. The syringe of any preceding claim, wherein (a) the body (2) is made out of a plastic material or glass and/or (b) the rod (26) is made from a plastic material.

14. The syringe of any preceding claim, wherein the syringe is silicone free or substantially silicone free.

15. The syringe of any one of claims 1-14, wherein the medicament comprises a biologic active which is an antibody (or fragment thereof) or a non-antibody protein.

16. The syringe of any one of claims 1-14, wherein the medicament comprises a VEGF antagonist.

17. The syringe of claim 16, wherein the VEGF antagonist is bevacizumab.

18. A syringe pack comprising a sealed package and a sterile syringe as defined in any preceding claim.

19. A method of assembling a syringe according to any one of claims 1 to 17, the method comprising steps of:

(i) providing a body (2) and a stopper (10), the body comprising an outlet (12) at an outlet end (14) and the stopper (10) being arranged within the body (2) such that a front surface of the stopper (10) and the body (2) define a variable volume chamber (18) from which a fluid can be expelled though the outlet (12), the outlet being releasably sealed and the variable volume chamber (18) containing the injectable medicament; and
(ii) providing a plunger (4) comprising a plunger contact surface (22) at a first end (24) and a rod (26) extending between the plunger contact surface (22) and a rear portion and arranging the plunger contact surface (22) and at least part of the plunger (4) within the body (2) without coupling the plunger (4) to the stopper (10).

20. The method of claim 19, further comprising step (iii) filling the variable volume chamber of the syringe with the injectable medicament, wherein steps (ii) and (iii) may be carried out in either order; and, optionally, wherein steps (i) and (iii) are carried out in a sterile, or substantially sterile, environment.

21. The method of claim 20, further comprising step (iv) packaging the assembled syringe in a substantially sealed package; and optionally, wherein, at some point between steps (iii) and (iv), the syringe is removed from the sterile, or substantially sterile, environment.

22. The method of claim 21, further comprising step (v) terminal sterilisation following packaging; for instance, wherein the terminal sterilisation step comprises Ethylene Oxide sterilisation or Hydrogen Peroxide sterilisation.

Patentansprüche

1. Terminal sterilisierte ophthalmische Spritze, wobei die Spritze einen Körper (2), einen Anschlag (10) und einen Kolben (4) umfasst, wobei der Körper einen Auslass (12) an einem Auslassende (14) umfasst und der Anschlag (10) innerhalb des Körpers (2) angeordnet ist, so dass eine Frontfläche (16) des Anschlags (10) und der Körper (2) eine Kammer (18) mit variablem Volumen definieren, aus der ein Fluid durch den Auslass (12) ausgestoßen werden kann, wobei der Kolben (4) eine Kolbenkontaktfläche (22) an einem ersten Ende (24) umfasst und eine Stange (26) sich zwischen der Kolbenkontaktfläche (22) und einem hinteren Anteil (25) erstreckt;

wobei die Kammer (18) mit variablem Volumen mit einem injizierbaren Medikament gefüllt ist, das einen Wirkstoff umfasst, der zur Behandlung einer Augenerkrankung geeignet ist;
dadurch gekennzeichnet, dass:

die Kolbenkontaktfläche (22) so angeordnet ist,
dass sie mit dem Anschlag (10) in Kontakt kommt,
jedoch nicht daran koppelt, so dass der Kolben (4) verwendet werden kann, um den Anschlag (10) in Richtung des Auslassendes (14) des Körpers (2) zu zwingen, wodurch das Volumen der Kammer (18) mit variablem Volumen reduziert wird, jedoch nicht, um den Anschlag (10) von dem Auslassende (14) weg zu bewegen; und
die Spritze so dimensioniert ist, dass sie ein maximales Nennfüllvolumen zwischen 0,25 mL und 0,75 mL oder zwischen 0,4 mL und 0,6 mL aufweist.

2. Spritze nach Anspruch 1, wobei der Auslass (12) reversibel versiegelt ist.

3. Spritze nach einem der vorhergehenden Ansprüche, wobei die Stange (26) mindestens eine Stangenschulter (32) umfasst, die von dem Auslassende (14) weg gerichtet ist, und wobei die Spritze einen Backstop einschließt, der an einem hinteren Anteil (25) des Körpers (2) angeordnet ist, wobei der Backstop eine Backstop-Schulter (34) einschließt, die zu dem Auslassende (14) gerichtet ist, um mit der Stangenschulter (32) zusammenzuwirken, um Bewegung der Kolbenstange (26) von dem Auslassende (14)

weg im Wesentlichen zu verhindern, wenn die Backstop-Schulter (34) und die Stangenschulter (32) in Kontakt sind.

4. Spritze nach einem der vorhergehenden Ansprüche, wobei (a) die Stangenschulter (32) innerhalb des Außendurchmessers der Stange (26) angeordnet ist; und/oder (b) die Stangenschulter (32) einen im Wesentlichen scheibenförmigen Anteil (46) auf der Stange (26) umfasst, wobei der scheibenförmige Anteil (46) gegebenenfalls Lücken (50) einschließt.

5. Spritze nach Anspruch 3 oder Anspruch 4, wobei der Backstop von der Spritze entfernbar ist; und wobei der Backstop gegebenenfalls ausgestaltet ist, um terminale Flansche (28) des Körpers im Wesentlichen sandwichartig zu umgeben.

6. Spritze nach einem der Ansprüche 3 bis 5, wobei, wenn die Kolbenkontaktfläche (22) in Kontakt mit dem Anschlag (10) angeordnet ist ist, und die Kammer mit variablem Volumen (18) an ihrem vorgesehenen Maximalvolumen ist, ein Spiel von nicht mehr als 2 mm zwischen der Stangenschulter (32) und der Backstop-Schulter (34) vorhanden ist.

7. Spritze nach einem der vorhergehenden Ansprüche, wobei: (a) die Kammer (18) mit variablem Volumen einen Innendurchmesser zwischen 3 mm und 6 mm aufweist; (b) die Spritze so dimensioniert ist, dass sie ein maximales Nennfüllvolumen zwischen 0,4 mL und 0,6 mL hat; und/oder (c) die Länge des Körpers (2) der Spritze kleiner als 70 mm ist, beispielsweise kleiner als 60 mm oder kleiner als 50 mm.

8. Spritze nach einem der vorhergehenden Ansprüche, wobei die Länge des Spritzenkörpers (2) zwischen 45 mm und 50 mm liegt, der Innendurchmesser zwischen 4 mm und 5 mm liegt, und das Füllvolumen zwischen 0,1 mL und 0,3 mL Flüssigkeit liegt.

9. Spritze nach einem der vorhergehenden Ansprüche, wobei: (a) der Anschlag (10) eine Versiegelungsfunktion bereitstellt, indem die Rückwand der Kammer (18) mit variablem Volumen mit einer fluiddichten Versiegelung definiert wird, die auch ein Sterilitätssiegel bereitstellt; und/oder (b) der Anschlag (10) eine oder mehrere umlaufende Rippen enthält, z. *B.* drei umlaufende Rippen (52, 54, 56).

10. Spritze nach einem der vorhergehenden Ansprüche, wobei der Anschlag (10) mindestens eine vordere umlaufende Rippe (52) und eine hintere umlaufende Rippe (56) enthält, die in einer Richtung entlang einer Achse (A) von dem Auslassende (14) des hinteren Endes (38) um mindestens 3 mm getrennt sind.

11. Spritze nach einem der vorhergehenden Ansprüche, wobei der Kolben (4), der nicht an den Anschlag (10) koppelt, einen Benutzer daran hindert, den Kolben (4) und einen damit verbundenen Anschlag (10) versehentlich zu bewegen und zu bewirken, dass unsterile Luft oder anderes Fluid in die Spritze gezogen wird, oder Bewegung des Anschlags (10) in einen nichtsterilen Bereich zu bewirken.

12. Spritze nach einem der vorhergehenden Ansprüche, wobei: (a) die Bewegung der Stange (26) von dem Auslassende (14) weg eingeschränkt ist; und/oder (b) die Kolbenkontaktfläche (22) eine im Wesentlichen planare Scheibe ist, und die Kolbenkontaktfläche (22) in Kontakt mit einer hinteren Fläche des Anschlags (10) ist.

13. Spritze nach einem der vorhergehenden Ansprüche, wobei (a) der Körper (2) aus einem Kunststoffmaterial oder Glas gefertigt ist, und/oder (b) die Stange (26) aus einem Kunststoffmaterial gefertigt ist.

14. Spritze nach einem der vorhergehenden Ansprüche, wobei die Spritze silikonfrei ist oder im Wesentlichen silikonfrei ist.

15. Spritze nach einem der Ansprüche 1 bis 14, wobei das Medikament einen biologischen Wirkstoff umfasst, der ein Antikörper (oder Fragment davon) ist, oder ein Protein ist, das kein Antikörper ist.

16. Spritze nach einem der Ansprüche 1 bis 14, wobei das Medikament einen VEGF-Antagonisten umfasst.

17. Spritze nach Anspruch 16, wobei der VEGF-Antagonist Bevacizumab ist.

18. Spritzenpack, umfassend eine versiegelte Packung und eine sterile Spritze wie in einem der vorhergehenden Ansprüche definiert.

19. Verfahren zum Montieren einer Spritze nach einem der Ansprüche 1 bis 17, wobei das Verfahren die Schritte umfasst:

(i) Bereitstellen eines Körpers (2) und eines Anschlags (10), wobei der Körper einen Auslass (12) an einem Auslassende (14) umfasst und der Anschlag (10) innerhalb des Körpers (2) angeordnet ist, so dass eine Frontfläche des Anschlags (10) und der Körper (2) eine Kammer (18) mit variablem Volumen definieren, aus der ein Fluid durch den Auslass (12) ausgestoßen werden kann, wobei der Auslass lösbar versiegelt ist und die Kammer (18) mit variablem Volumen das injizierbare Medikament enthält; und
(ii) Bereitstellen eines Kolbens (4), der eine Kolbenkontaktfläche (22) an einem ersten Ende

(24) und eine Stange (26) umfasst, die sich zwischen der Kolbenkontaktfläche (22) und einem hinteren Anteil erstreckt und die Kolbenkontaktfläche (22) und mindestens einen Teil des Kolbens (4) innerhalb des Körpers (2) anordnet, ohne den Kolben (4) an den Anschlag (10) zu koppeln.

20. Verfahren nach Anspruch 19, des Weiteren umfassend Schritt (iii) des Füllens der Kammer mit variablem Volumen von der Spritze mit dem injizierbaren Medikament, wobei Schritte (ii) und (iii) in beliebiger Reihenfolge durchgeführt werden können; und wobei die Schritte (i) und (iii) gegebenenfalls in einer sterilen oder im Wesentlichen sterilen Umgebung ausgeführt werden.

21. Verfahren nach Anspruch 20, des Weiteren umfassend Schritt (iv) des Verpackens der montierten Spritze in einer im Wesentlichen versiegelten Packung; und wobei gegebenenfalls an irgendeinem Punkt zwischen den Schritten (iii) und (iv) die Spritze aus der sterilen oder im Wesentlichen sterilen Umgebung entfernt wird.

22. Verfahren nach Anspruch 21, des Weiteren umfassend Schritt (v) der terminalen Sterilisation nach dem Verpacken; beispielsweise wobei der terminale Sterilisationsschritt Ethylenoxidsterilisation oder Wasserstoffperoxidsterilisation umfasst.

Revendications

1. Seringue ophtalmique à terminaison stérilisée, la seringue comprenant un corps (2), un bouchon (10) et un plongeur (4), le corps comprenant une sortie (12) à une extrémité de sortie (14) et le bouchon (10) étant disposé à l'intérieur du corps (2) de telle sorte qu'une surface avant (16) du bouchon (10) et du corps (2) définissent une chambre à volume variable (18) depuis laquelle un fluide peut être expulsé à travers la sortie (12), le plongeur (4) comprenant une surface de contact de plongeur (22) à une première extrémité (24) et une tige (26) s'étendant entre la surface de contact de plongeur (22) et une portion arrière (25) ;

dans laquelle la chambre à volume variable (18) est remplie d'un médicament injectable comprenant un principe actif approprié pour le traitement d'une maladie oculaire ;
caractérisée en ce que :

la surface de contact de plongeur (22) est conçue pour venir en contact avec le bouchon (10) mais pas pour s'accoupler avec celui-ci, de telle sorte que le plongeur (4) puisse être utilisé pour forcer le bouchon (10) vers l'extrémité de sortie (14) du corps (2),
en réduisant le volume de la chambre à volume variable (18), mais pas pour déplacer le bouchon (10) à l'écart de l'extrémité de sortie (14) ; et
la seringue est dimensionnée de manière à avoir un volume de remplissage maximal nominal entre 0,25 ml et 0,75 ml, ou entre 0,4 ml et 0,6 ml.

2. Seringue selon la revendication 1, dans laquelle la sortie (12) est scellée de manière réversible.

3. Seringue selon l'une quelconque des revendications précédentes, dans laquelle la tige (26) comprend au moins un épaulement de tige (32) orienté à l'écart de l'extrémité de sortie (14) et la seringue comporte une butée arrière agencée au niveau d'une portion arrière (25) du corps (2), la butée arrière comportant un épaulement de butée arrière (34) orienté vers l'extrémité de sortie (14) de manière à coopérer avec l'épaulement de la tige (32) pour empêcher substantiellement un mouvement de la tige de plongeur (26) à l'écart de l'extrémité de sortie (14) lorsque l'épaulement de butée arrière (34) et l'épaulement de tige (32) sont en contact.

4. Seringue selon l'une quelconque des revendications précédentes, dans laquelle (a) l'épaulement de la tige (32) est disposé dans le diamètre externe de la tige (26) ; et/ou (b) l'épaulement de la tige (32) comprend une portion substantiellement en forme de disque (46) sur la tige (26), la portion en forme de disque (46) comprenant facultativement des espaces (50).

5. Seringue selon la revendication 3 ou la revendication 4, dans laquelle la butée arrière est amovible depuis la seringue ; et facultativement dans laquelle la butée arrière est configurée pour prendre substantiellement en sandwich les brides terminales (28) du corps.

6. Seringue selon l'une quelconque des revendications 3 à 5, dans laquelle, lorsqu'elle est disposée avec la surface de contact de plongeur (22) en contact avec le bouchon (10) et que la chambre à volume variable (18) est à son volume maximal prévu, il existe un jeu inférieur ou égal à 2 mm entre l'épaulement de tige (32) et l'épaulement de butée arrière (34).

7. Seringue selon l'une quelconque des revendications précédentes, dans laquelle : (a) la chambre à volume variable (18) a un diamètre interne entre 3 mm et 6 mm ; (b) la seringue est dimensionnée de manière à avoir un volume de remplissage maximal nominal entre 0,4 ml et 0,6 ml ; et/ou (c) la longueur du

corps (2) de la seringue est inférieure à 70 mm, par exemple inférieure à 60 mm ou inférieure à 50 mm.

8. Seringue selon l'une quelconque des revendications précédentes, dans laquelle la longueur du corps de seringue (2) est entre 45 mm et 50 mm, le diamètre interne est entre 4 mm et 5 mm, et le volume de remplissage est entre 0,1 ml et 0,3 ml de liquide.

9. Seringue selon l'une quelconque des revendications précédentes, dans laquelle : (a) le bouchon (10) assure une fonction d'étanchéité en définissant l'arrière de la chambre à volume variable (18) avec un joint étanche aux fluides, qui forme également un joint stérile ; et/ou (b) le bouchon (10) contient une ou plusieurs nervures circonférentielles, par exemple trois nervures circonférentielles (52, 54, 56).

10. Seringue selon l'une quelconque des revendications précédentes, dans laquelle le bouchon (10) contient au moins une nervure circonférentielle avant (52) et une nervure circonférentielle arrière (56) qui sont séparées dans une direction le long d'un axe (A) depuis l'extrémité de sortie (14) vers l'extrémité arrière (38) d'au moins 3 mm.

11. Seringue selon l'une quelconque des revendications précédentes, dans laquelle le plongeur (4) qui ne s'accouple pas au bouchon (10) empêche qu'un utilisateur déplace accidentellement le plongeur (4) et un bouchon relié à celui-ci (10) et provoque l'aspiration d'air non stérile ou de tout autre fluide dans la seringue, ou provoque le déplacement du bouchon (10) vers une zone non stérile.

12. Seringue selon l'une quelconque des revendications précédentes, dans laquelle : (a) le mouvement de la tige (26) à l'écart de l'extrémité de sortie (14) est limité ; et/ou (b) la surface de contact de plongeur (22) est un disque substantiellement plan, et la surface de contact de plongeur (22) est en contact avec une surface arrière du bouchon (10).

13. Seringue selon l'une quelconque des revendications précédentes, dans laquelle (a) le corps (2) est fait d'une matière plastique ou de verre et/ou (b) la tige (26) est faite d'une matière plastique.

14. Seringue selon l'une quelconque des revendications précédentes, dans laquelle la seringue est exempte de silicone ou substantiellement exempte de silicone.

15. Seringue selon l'une quelconque des revendications 1 à 14, dans laquelle le médicament comprend un principe actif biologique qui est un anticorps (ou un fragment de celui-ci) ou une protéine non-anticorps.

16. Seringue selon l'une quelconque des revendications 1 à 14, dans laquelle le médicament comprend un antagoniste du VEGF.

17. Seringue selon la revendication 16, dans laquelle l'antagoniste du VEGF est le bévacizumab.

18. Emballage de seringue comprenant un emballage scellé et une seringue stérile selon l'une quelconque des revendications précédentes.

19. Procédé d'assemblage d'une seringue selon l'une quelconque des revendications 1 à 17, le procédé comprenant les étapes consistant à :

(i) fournir un corps (2) et un bouchon (10), le corps comprenant une sortie (12) à une extrémité de sortie (14) et le bouchon (10) étant disposé à l'intérieur du corps (2) de telle sorte qu'une surface avant du bouchon (10) et le corps (2) définissent une chambre à volume variable (18) à partir de laquelle un fluide peut être expulsé à travers la sortie (12), la sortie étant scellée de manière amovible et la chambre à volume variable (18) contenant le médicament injectable ; et
(ii) fournir un plongeur (4) comprenant une surface de contact de plongeur (22) à une première extrémité (24) et une tige (26) s'étendant entre la surface de contact de plongeur (22) et une partie arrière et disposer la surface de contact du plongeur (22) et au moins une partie du plongeur (4) à l'intérieur du corps (2) sans accoupler le plongeur (4) au bouchon (10).

20. Procédé de la revendication 19, comprenant en outre l'étape (iii) consistant à remplir la chambre à volume variable de la seringue avec le médicament injectable, dans lequel les étapes (ii) et (iii) peuvent être réalisées dans n'importe quel ordre ; et, facultativement, dans lequel les étapes (i) et (iii) sont réalisées dans un milieu stérile, ou substantiellement stérile.

21. Procédé selon la revendication 20, comprenant en outre l'étape (iv) consistant à emballer la seringue assemblée dans un emballage substantiellement scellé ; et facultativement, dans lequel, à un certain point entre les étapes (iii) et (iv), la seringue est retirée de l'environnement stérile, ou substantiellement stérile.

22. Procédé de la revendication 21, comprenant en outre l'étape (v) de stérilisation terminale après l'emballage ; par exemple, dans lequel l'étape de stérilisation finale comprend la stérilisation à l'oxyde d'éthylène ou la stérilisation au peroxyde d'hydrogène.

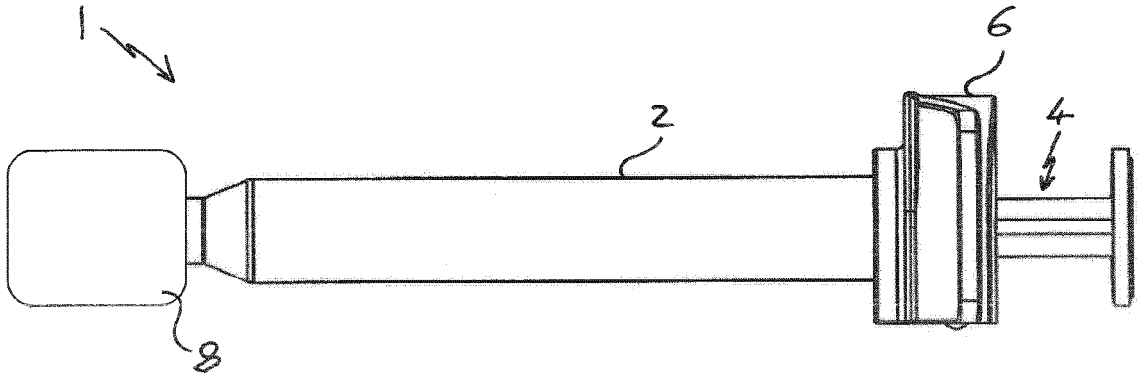

Fig 1

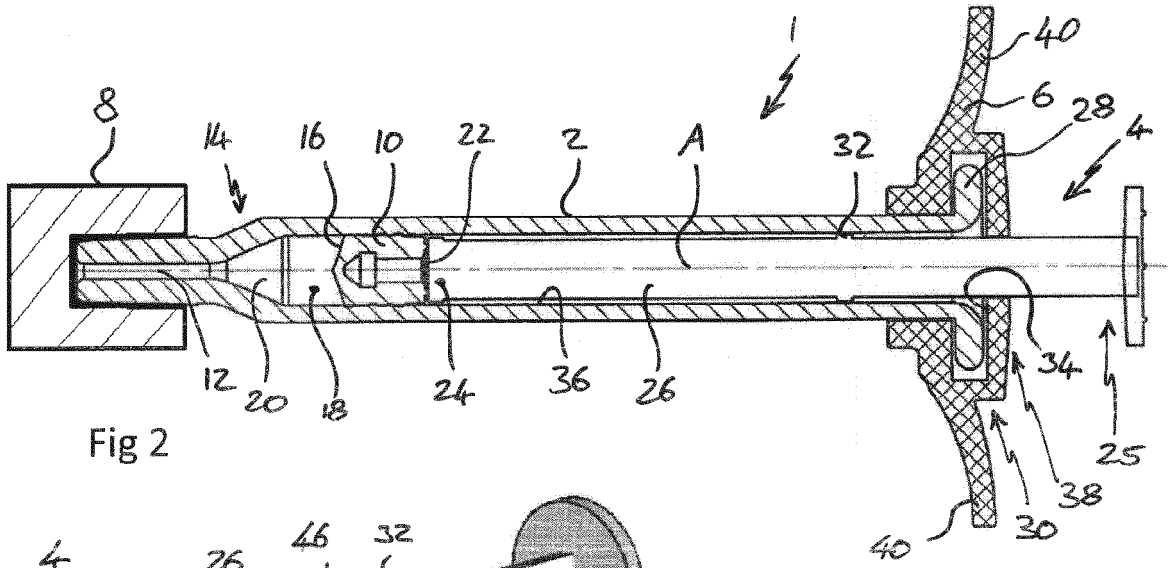

Fig 2

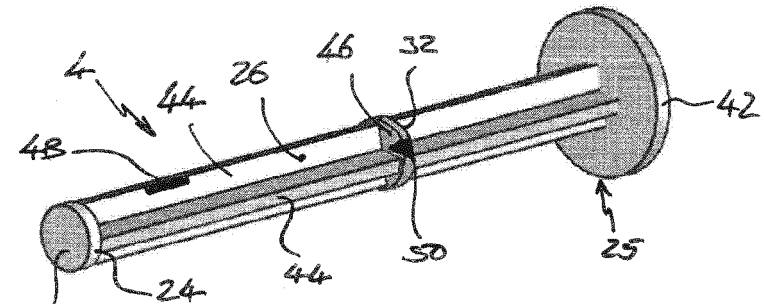

Fig 3

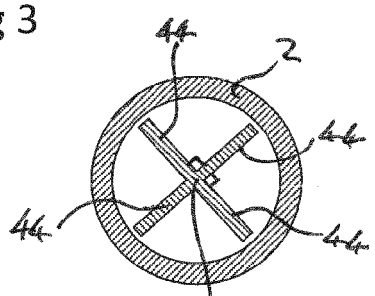

Fig 4

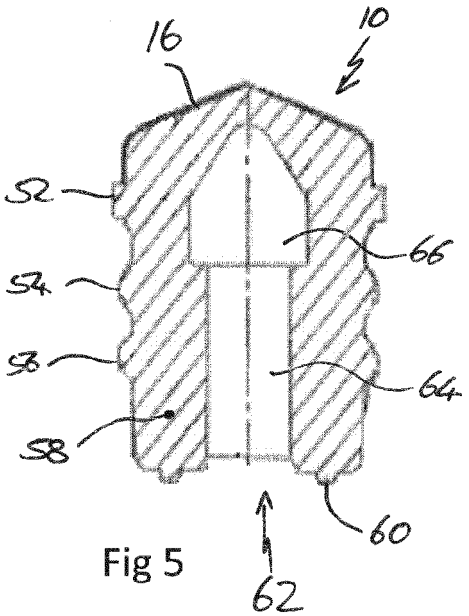

Fig 5

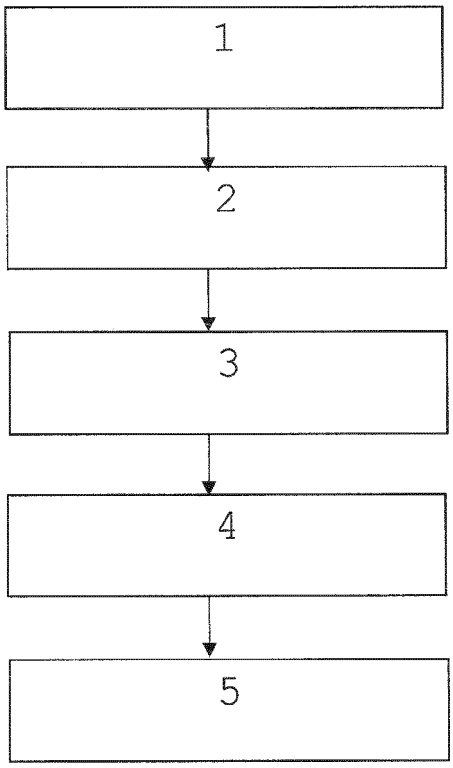

Fig 6

REFERENCES CITED IN THE DESCRIPTION

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